

- D1*
- (a) reacting the initial library with mounted tissue of one or more *in situ* target structure(s);
 - (b) eluting directly and recovering the unbound phage particles from phage particles which bound to the target structure(s), wherein the recovered unbound phage particles comprise a first enriched library, not capable of binding to the target structure(s);
 - (c) recovering the bound phage particles by cleaving said bound phage particles from the cells, and wherein the bound phage particles comprise a second enriched library capable of binding the target structure(s);
 - (d) amplifying either enriched library; and
 - (e) purifying individual elements of either enriched library and identifying the desired phage particle(s) which exhibit desired binding behavior *in vivo* or *in situ* against the target structure(s) of interest after steps (a) through (d).

D1

2. (Amended) The method as claimed in claim 1 further comprising repeating steps (a) through (c) against tissue, which tissue is positive for the target structure(s), to positively enrich for binding phage particles.

3. (Amended) The method as claimed in claim 1 further comprising repeating steps (a) through (d) against further tissue which does not display the target structure(s), effecting a negative enrichment.

4. (Three Times Amended) The method as claimed in claim 1 further comprising repeating steps (a) through (d).

6. (Twice Amended) The method as claimed in claim 1, wherein the target structure is displayed as an authentic cellular epitope.

D2

7. (Three Times Amended) The method as claimed in claim 1, wherein the target is displayed as an authentic phenotypic epitope.

13 9. (Amended) The method as claimed in claim 7, wherein the authentic *in vivo* and/or *in situ* phenotypes are the result of a physiological process, a pathological process, a cell and/or tissue development and differentiation, or a drug response, or a naturally occurring degradation process. E

10. (Amended) The method as claimed in claim 9, wherein the pathological process is an inflammation, a secondary tumor deposit, or tumor vasculature.

17. (Twice Amended) The method as claimed in claim 7, wherein the set of target structures are target structures from a whole cell.

18. (Twice Amended) The method as claimed in claim 7, wherein the target structure is located in a cell surface.

19. (Twice Amended) The method as claimed in claim 7, wherein the target structure is located intracellularly of a cell surface. E

14 20. (Twice Amended) The method as claimed in claim 7, wherein the target structure is located extracellularly of a cell surface.

21. (Twice Amended) The method as claimed in claim 7, wherein the target structure is located intranuclear of a nuclear membrane.

22. (Three-Times-Amended) The method as claimed in claim 7, wherein the target structure(s) is a simple or complex epitope comprising ligand(s), (a) receptor(s), (an) adhesion molecule(s), (a) matrix associated molecule(s), other than luminal vasculature targets.

23. (Twice Amended) The method as claimed in claim 22, wherein the target structure comprises a protein, a carbohydrate, a nucleic acid, or a lipid.

24. (Three Times Amended) The method as claimed in claim 1, wherein the tissue is obtained by a histological technique.

25. (Amended) The method as claimed in claim 24, wherein the histological technique comprises freezing and/or fixation, and sectioning of the tissue.

D4
cont
26. (Amended) The method as claimed in claim 24, wherein the tissue is pre-treated with enzyme or by chemical means.

27. (Amended) The method as claimed in claim 26, wherein the enzyme pre-treatment is performed with a protease and/or a polysaccharase and/or a ribonuclease, and/or a nuclease.

D5
29. (Amended) The method as claimed in claim 1, wherein the tissue is a suspension of bone marrow cells, lymph cells, sperm cells, or cells from cerebrospinal fluid.

33. (Amended) The method as claimed in claim 1, wherein the *in situ* target comprises cells suspended from the tissue.

D6
34. (Twice Amended) The method as claimed in claim 1, wherein the target structure is a molecule released from cells.

35. (Amended) The method as claimed in claim 34, wherein the cells are tumor cells.

36. (Amended) The method as claimed in claim 34, wherein the molecule is released actively.

37. (Twice Amended) The method as claimed in claim 34, wherein the molecule is released passively.

38. (Amended) The method as claimed in claim 1, wherein the initial library is a naive, synthetic, or semi-synthetic antibody library.

39. (Amended) The method as claimed in claim 1, wherein the initial library is a combinatorial library.

40. (Amended) The method as claimed in claim 39, wherein the combinatorial library is a library produced by immunization against one or more displayed target structures.

41. (Amended) The method as claimed in claim 39, wherein the combinatorial library is a chemical library.

42. (Amended) The method as claimed in claim 1, wherein the step of acquiring binding structures further comprises identifying, producing, characterizing, selecting, enriching, or defining such structures.

43. (Twice Amended) The method as claimed in claim 1, wherein the step of ~~amplifying bound binding structures further comprises~~ amplifying the bound binding structures using bacterial cells, PCR synthesis or chemical synthesis.

44. (Amended) The method as claimed in claim 1, wherein linkage between binding structure(s) and genetic and/or other identifying information comprises coded beads or polysomes.

45. (Amended) The method as claimed in claim 1, wherein linkage between binding structure(s) and genetic and/or other identifying information comprises particles of filamentous phage or of any other virus.

46. (Amended) The method as claimed in claim 45, wherein the filamentous phage is bacteriophage M13.

47. (Amended) The method as claimed in claim 1, wherein the step of recovering bound binding structures comprises cleavage.

48. (Amended) The method as claimed in claim 47, wherein the cleaved bound binding structure maintains amplification ability.

49. (Twice Amended) The method as claimed in claim 45, wherein the cleavage site is between the binding structure and a phage protein.

50. (Amended) The method as claimed in claim 49, wherein the phage protein is minor coat protein pIII.


51. (Amended) The method as claimed in claim 47, wherein cleavage occurs at a protease recognition site.

52. (Twice Amended) The method as claimed in claim 51, wherein the cleavage site is Ala-Ala-His-Tyr and the protease is Ala64-subtilisin.



53. (Twice Amended) The method as claimed in claim 51, wherein the cleavage site is Ile-Glu-Gly-Arg and the protease is blood clotting factor Xa.


54. (Amended) The method as claimed in claim 1, wherein the step of recovering bound binding structures is effected by means of a chemically based elution.

55. (Amended) The method as claimed in claim 54, wherein the elution is performed with an acid or alkaline solution.

 56. (Amended) The method as claimed in claim 6, wherein the antibody is a scFv C215 antibody fragment.

57. (Amended) The method as claimed in claim 7, wherein the target structure is an epitope on GA733-2 epithelial glycoprotein expressed in colorectal carcinoma.

 Please add new claim 65: 

 65. (New) The method of claim 55, wherein the alkaline solution is triethylamine.
